UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,248	09/28/2004	Shunichi Kuroda	12480-000066/US	4497

30593 7590 07/13/2007

HARNESS, DICKEY & PIERCE, P.L.C.
P.O. BOX 8910
RESTON, VA 20195

EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
07/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,248	KURODA ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *7 and 13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-12* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/28/04&9/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I, Claims 1-6 and 8-12, without traverse, filed on May 2, 2007, is acknowledged. The requirement is made FINAL.

2. Accordingly Claims 1-22 are pending. Claims 7 and 13-22 are withdrawn as non-elected. Claims 1-6 and 8-12 are considered in this Office action.

Information Disclosure Statement

3. The information disclosure statement submitted on December 28, 2004, is in compliance with the provisions of 37 CRF 1.97. Accordingly, the information disclosure statement has been considered by the examiner. An initialed and dated copy of the Applicant's IDS form 1449 is attached to the instant Office action.

Claim Rejections - 35 USC § 112, first paragraph-Scope of enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-6 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for constructing HBsAg particles, does not reasonably provide enablement for making any other nanoparticles containing any undefined molecules, and does not reasonably provide enablement for using un characterized nanoparticles containing any undefined molecules as a drug. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech Inc. v. Novo Nordisk 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); In re Wright 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); In re Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in In re Wands 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

9. Claims 1-6 and 8-12 are directed to a drug comprising a substance to be transferred into a cell for treatment of a disease encapsulated in a hollow nanoparticle containing a particle-forming protein, the nanoparticle displaying a molecule, such as a

growth factor, which binds with a particular molecule on a cell surface, wherein the protein is a modified hepatitis B virus surface antigen protein, wherein the substance to be transferred into a cell is a gene, wherein the gene is a cancer-treating gene, wherein the gene is thymidine kinase (HSV1 tk) gene of herpes simplex virus type 1, wherein said drug is administered to a human body through intravenous injection.

10. Since there are no structural limitations to "a particle-forming protein" and a "substrate" and "displaying molecule" in Claim 1, the scope of the claims encompasses "a drug" comprising any nanoparticles that contain any substances. First of all, to put drug discovery and development in the right perspective, the state of the art indicates "The process of drug discovery and development is a long, complex and multi-stage process where odds of success, in retrospect, are low. For drug, in general, only 20% of drug discovery projects leads to a clinical candidate and only 10% of compounds that enter clinical development achieve registration" (Pauwels, 2006). More importantly, Pauwels points out: "Analysis of the reasons for apparently low and even declining success rate reveals that projects mainly fail because drug candidates prove inactive in animal models or in patients, display unacceptable toxicity or cause undesirable side-effects upon *in vivo* administration" (Pauwels, 2006). Thus, the state of the art has shown that drug development is unpredictable, neither is the alleged drug comprising any nanoparticles that contain any substances.

11. The state of prior art also teaches that it is unpredictable to assemble a foreign protein or substance into a viral particle because formation of a viral particle requires specific packaging/assembly signals and has restrictions on inserted sequences and insertion sizes. The structure of foreign substances can affect particle formation. For

example, Ward et al (Virus Genes, Vol. 23: p. 97-104, 2001) tried to package the hepatitis C virus (HCV) core protein into HBsAg particles. Ward *et al* found that only limited chimeric proteins were packaged into viral particles, due to poor expression and the size limit to the insert (see in particular the abstract and Fig. 3). Therefore, it is unpredictable in the art to predict the outcome of trying to assemble uncharacterized substances into any particle-forming proteins. The specification has provided little guideline as to what are the structural requirements for "a substance" to be fused or packaged into any particle-forming proteins.

12. Furthermore, Claims 3-5 are directed to the drug as set forth in Claim 1, wherein the substance to be transferred into a cell is a gene, a cancer-treating gene or HSV-1 tk gene. Since the claim language is closed, Claims 3-5 read on a nanoparticle containing a particle-forming protein in which only a gene, a cancer-treating gene or HSV-1 tk gene (as a substance) is encapsulated. However, it is known in the art that a gene by itself, without a gene expression control unit, such as a promoter, start/stop and polyA signals, etc., cannot be sufficiently expressed. Thus, the alleged "substance to be transferred into a cell" (Calim1) cannot be made and utilized "for treatment of a disease" (Claim 1).

13. *In re Fisher*, 427 F.2d 833,166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the specification has disclosed how to make HBsAg-EGF particles and a complex of HBsAg-EGF with HSV1-tk plasmid. The specification, however, does not show how to assemble uncharacterized substances into any other particle-forming proteins. The specification has provided little guideline what are the structural requirements for encapsulating a substance into any nanoparticle. Thus, one of

ordinary skill in the art would not know how to make a nanoparticle comprising any substance.

14. Moreover, while the specification disclosed that the complex of HBsAg-EGF with HSV1-tk plasmid reduced the size of a tumor in nude rats, it has not provided *in vivo* or *in vitro* data that alleged drugs of any nanoparticles containing any substances can be effective in treating any diseases, providing clinical benefit. The specification fails to show the correlation between the diseases as capable of treatment by alleged drugs of nanoparticles comprising an undefined substance. In the absence of evidence, one of skill in the art is unable to fully predict possible clinical application and benefit of the alleged drugs, therefore, would not know how to use the alleged drugs.

15. Since the scope of Claims 1-6 and 8-12 clearly covers a very broad of alleged drugs comprising undefined nanoparticles for treating un-specified diseases in human, in order for the full breadth of the invention to be enabled, a skilled artisan would have to make and test all particle-forming proteins to see if they can encapsulate any substance, and test them to see if they can be "a drug" for treating undefined diseases, such as all unspecified cancers. Such drug screening would entail an undue amount of experimentation. In view of the empirical and unpredictable nature of drug development and lack of guidance and working examples in the specification, one skilled in the art would not know how to make and use alleged drugs of the instant invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that

form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosenfeld (1997; Annals of Surgery 1997; 225(5):609-618).

18. Claims 1 and 6 are directed to a drug comprising a substance to be transferred into a cell for treatment of a disease encapsulated in a hollow nanoparticle containing a particle-forming protein, the nanoparticle displaying a molecule, such as a growth factor, which binds with a particular molecule on a cell surface.

19. Rosenfeld teaches an adenoviral particle comprising HSV1 tk gene (AdCMVHSV-1tk) (pp 610 and 611). Rosenfeld shows that Ad/HSV-1tk particles are highly transducible to human pancreatic carcinoma cells and the resulting carcinoma cells expressing HSV-1 tk protein is more sensitive to chemotherapy agent ganciclovir (GCV) (p.611). Rosenfeld teaches that in vivo administration of AdCMVHSV-1tk and GCV results in reduced tumor burden (p. 614 and 615). Rosenfeld suggests a strategy for human pancreatic carcinoma using HSV-tk and GCV in molecular chemotherapy (Abstract).

20. Since AdCMVHSV-1tk particle is "a nanoparticle" which contains a particle-forming protein, and displays a molecule that binds with a particular molecule on a cell surface, wherein the HSV-1 tk substance transferred into a cell can be used for treatment of a cancer, Rosenfeld's AdCMVHSV-1tk particles meet the structural limitations in the claims. Thus, the instant Claim 1 is anticipated by Rosenfeld.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 1-6 and 8-12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claim 1 of **10/509, 247**, Claims 1-7 of **10/509, 252**, and Claims 28, 30, 31, 33, 36, 37, 40 of co-pending application of **10/220,125**. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to the same process using the same products.

23. Claims 1-6 and 8-12 are directed to a drug comprising a substance to be encapsulated in a hollow nanoparticle containing a particle-forming protein, transferred into a cell for treatment of a disease, the nanoparticle displaying a molecule, such as a growth factor, which binds with a particular molecule on a cell surface, wherein the

protein is a modified hepatitis B virus surface antigen protein, wherein the substance to be transferred into a cell is a gene, wherein the gene is a cancer-treating gene, wherein the gene is thymidine kinase (HSV1 tk) gene of herpes simplex virus type 1, wherein said drug is administered to a human body through intravenous injection.

24. Claim 1 of **10/509, 247** is directed to a pharmaceutical compound comprising: a particle-forming protein capable of recognizing a hepatocyte; and a disease-treating target-cell-substance fused to the particle-forming protein, wherein the protein forms a nanoparticle encapsulating the target-cell-substance: the protein is a hepatitis B virus surface-antigen protein; and the target-cell substance is selected from the group consisting of interferons, hepatocyte growth factors, and interleukins.

25. Claims 1-7 of **10/509, 252** are directed to a drug that comprises hollow nanoparticles of a particle-forming protein, the hollow nanoparticles having an ability to recognize a hepatocyte, and encapsulating a substance to be transferred to a cell for treatment of a hepatic disease, wherein the protein comprises a hepatitis B virus surface-antigen protein, wherein the hepatic disease-treating substance comprises a gene, wherein the gene comprises a cancer-treating gene, wherein the gene comprises a thymidine kinase (HSVltk) gene derived from herpes simplex virus, wherein the drug is administered to the human body through intravenous injection.

26. Claims 28, 30, 31, 33, 36, 37, and 40 of **10/220, 125** are directed to a transporter of substances for transferring substances into target cells or tissues, comprising a hollow nanoparticle obtained by expressing a HBsAg protein or mutant thereof capable of forming a particle in a eucaryotic cell, and a biorecognition molecule which is incorporated in the hepatitis B virus surface antigen protein or mutant thereof, wherein

the biorecognition molecule is selected from the group consisting of cell function-regulating molecules, cell or tissue-recognizing molecules, and antibodies and further wherein the biorecognition molecule is recognized by target cells or tissues into which the substance is introduced, and incorporated therein is a substance to be introduced into the target cells or tissues, wherein the substance is selected from the group consisting of genes, natural or synthetic proteins, oligonucleotides, peptides, drugs and natural or synthetic compounds, wherein the biorecognition molecule is selected from a group consisting of growth factors, cytokines, cell surface antigens, tissue specific antigens, receptors and antibodies, wherein the substance to be introduced into cells is a gene, wherein the substance to be introduced into cells is selected from the group consisting of DNAs, RNAs, proteins, peptides and drugs, wherein the substance to be introduced into cells is selected from the group consisting of DNAs and RNAs, wherein the substance to be introduced into cells is a drug.

27. Since the four sets of claims are all drawn to a nanoparticle comprising HBsAg, a compound that recognizes/targets cells and a substance of DNA or RNA, they clearly are the same compounds. Therefore, "a drug" of the instant Claims 1-6 and 8-12 is not patentably distinct from those of 10/509,247, 10/509,252 and 10/220,125.

Remarks

28. No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status

information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph.D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Bo Peng, Ph.D.
June 28, 2007

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600